approximately 85% of cases. TSC1 for approximately 30% and TSC2 69% of confirmed cases.

Pathology

The gene product for *TSC1* is hamartin and for *TSC2*, tuberin. Both gene products interact with the mammalian target of rapamycin (mTOR), which is essential in cell growth, proliferation, and angiogenesis. Hamartin and tuberin join to form a combined tumor suppressor complex (TSC1:TSC2 complex) that acts to inhibit mTOR signaling. Mutations that impair function of the TSC1:TSC2 complex lead to unregulated growth and proliferation.

Clinical Presentation

Like NF1, TSC has variable presentation depending on the location and extent of lesions. The organs most affected include the brain (cortical tubers, subependymal giant cell astrocytomas [SEGAs]), heart (cardiac rhabdomyomas), skin (facial angiofibromas, hypomelanotic skin macules or "ash leaf spot," shagreen patches, and subungual fibromas), kidney (renal angiomyolipoma), eye (retinal hamartoma), and lung (pulmonary lymphangioleiomyomatosis). Seizures, most commonly infantile spasms, are the usual early clinical presentation.

Diagnosis/Differential

The spectrum of tumors seen in TSC patients can also be seen in isolation. Biopsy may be needed to distinguish facial angiofibromas from acne and other skin lesions.

Treatment

Treatment is directed toward the epilepsy, especially for infantile spasms. A surgical approach may be necessary for intractable epilepsy. SEGAs are slow growing tumors that may enlarge and cause obstruction, especially during adolescence and early adulthood. Surgical treatment of SEGAs causing hydrocephalus can be effective but associated with significant morbidity. Everolimus is a pharmacologic mTOR inhibitor that is effective at reducing the size and growth of SEGAs and is useful for delaying the need for surgery or in those cases where surgery is not an option. Renal angiomyolipomas are prone to hemorrhage and may need to be resected, and pulmonary lymphangioleiomyomatosis may cause life-threatening complications. These renal and pulmonary tumors may also respond to the mTOR inhibitors, everolimus and sirolimus. Cognitive disability may require special education.

Prognosis

The variability in outcome depends on the extent and type of presenting symptoms. Refractory seizures, developmental delays, and CNS lesions have poor prognoses. The development of renal angiolipomas, especially multiple tumors, is also associated with poorer outcome.

Sturge-Weber Syndrome (SWS)

Definition/Epidemiology

SWS is variably characterized by an upper facial vascular nevus (port-wine stain), leptomeningeal angiomatos (cerebral venous malformation), and glaucoma with ocular capillary malformations. The disorder occurs sporadically in less than 1 in 20,000 births.

Pathology

The port-wine stain represent a collection of congested capillaries of subepidermal tissue. If there is an associated leptomeningeal vessel abnormality, it tends to be ipsilateral to the port-wine stain. The leptomeningeal vascular malformation makes the underlying brain susceptible to injury, possibly from venous stasis and abnormal perfusion. Cortical injury can lead to increased susceptibility to seizures, which in turn can increase the metabolic demands of already poorly perfused tissue.

Clinical Presentation

Clinical features include focal epilepsy, cognitive impairment, and, less frequently, hemiparesis, hemianopia, and glaucoma.

Diagnosis/Differential

The diagnosis is usually made by observing a port-wine stain in the cranial nerve V1 distribution with neuroimaging confirmation of the intracranial abnormality. Magnetic resonance imaging is a more reliable tool for diagnosis because calcifications on computed tomographic scans are classic but unnecessary for the diagnosis. However, 80% of people with a facial port-wine stain have no associated brain involvement. SWS should be distinguished from other disorders involving abnormal intracranial vessels and intractable seizures and neurologic dysfunction. These include moyamoya disease, other vascular malformations, and tuberous sclerosis.

Treatment

Aspirin (3-5 mg/kg/day) may reduce the frequency of stroke-like events. Aggressive treatment of seizures is indicated as well. If antiepileptic drugs do not control seizures, surgical excision of epileptogenic areas may be indicated. Laser treatment of the port-wine stain is of cosmetic benefit. Patients require regular ophthalmologist visits to screen for and surgically treat glaucoma.

Prognosis

Prognosis depends on the degree of underlying intellectual and developmental disability and control of seizures.

Von Hippel-Lindau Disease (Central Nervous System Angiomatosis)

Definition/Epidemiology

Von Hippel–Lindau (VHL) disease is an autosomal-dominant disorder caused by a defective tumor suppressor gene, *VHL*, associated with a variety of vascular tumors in multiple organs, including cerebellar and retinal hemangioblastomas and renal cell carcinomas. Incidence is 1/36,000.

Pathology

VHL is a tumor suppressor gene and increases susceptibility to various vascular tumors.